

## REMARKS

The amendments and remarks herein are made in addition to those in the after-final response filed March 15, 2007. The applicants request entry of the amendments made in the March 15 response in addition to the amendment to claim 18 herein. The Advisory Action mailed March 27, 2007, indicated that the rejection under 35 U.S.C. § 112, second paragraph, have been overcome. Thus, the only outstanding rejection is a 35 U.S.C. § 103, rejection against the pending claims.

### **Claim rejections under 35 U.S.C. § 103(a)**

Claims 18-20, 28, 29, 33, 34, 37, and 38 were rejected in the December 21, 2006, final Office Action, and claims 18-20 and 33-38 stand rejected in both the March 27, 2007, and May 1, 2007, Advisory Actions, under 35 U.S.C. § 103(a) as allegedly being obvious over Elbashir *et al.* (The EMBO Journal, Vol. 20, No. 23, pages 6877-6888, 2001), in view of Matulic-Adamic *et al.* (US 5,998,203), Parrish *et al.* (molecular Cell, Vol. 6, pages 1077-1087, 2000), and Crooke (US 5,898,031).

The applicants maintain their previous arguments regarding the non-obviousness of the pending claims. The following remarks are provided specifically in response to the Advisory Actions mailed on March 27, 2007, and May 1, 2007.

Denying the applicants' assertion that the underlying premise of the obviousness rejection is the unstated and unsubstantiated assumption that all nucleic acid technology is essentially the same and interchangeable, the Advisory Actions stated that that the examiner had not asserted that chemical modifications employed in antisense and ribozyme technology could be used freely and without limitation in siRNA technology. According to the Advisory Actions, the Examiner rather asserted that it would have been obvious to one of ordinary skill in the art to use the modifications of antisense and ribozyme technology in siRNA. But, as the applicants have repeatedly argued, at the February 20, 2002, priority date of the present claims, it was not believed that such modifications would be necessary for double stranded constructs. Nor was it known or predictable, given how little was understood regarding the mechanism of siRNA, whether modifications from the antisense and ribozyme arts would impart desired properties (such as increasing stability) without interfering with the ability of the double stranded constructs to induce RNAi.

Significantly, none of the cited references provides any guidance regarding whether the modifications recited in the present claims would impart desired properties (e.g., increased stability) without detrimentally affecting the functionality of the molecule.

The Advisory Actions further alleged that Elbashir is "direct evidence that chemical modifications utilized in antisense and ribozyme technology were utilized with siRNA's as well," before this application's priority date. (*See* Advisory Actions). But, as repeatedly noted, Elbashir reported marginal success, which would not have informed the particular chemical modification patterns recited in the present claims, finding that the ability to induce RNAi was retained only when 2 or 4 ribonucleotides at the siRNA 3'-ends were replaced with deoxy ribonucleotides; replacement of all ribonucleotides on one or both strands with deoxy ribonucleotides or 2'-*O*-methyl substituted nucleotides abolished activity. And even to the extent that activity was retained with the 3'-end deoxy substitutions, siRNA activity tended to decrease with more substitutions. Moreover, Elbashir expressly cautioned against the use of other than two 3'-end deoxy modifications. Therefore, rather than providing the "direct evidence that chemical modifications ... were utilized ... with siRNA's as well," Elbashir is evidence that at the time, those skilled in the art believed that the specific modifications (including the specific terminal caps at both the 5'- and 3'- ends of the first strand, and optionally at the 3'-end of the second strand, of a duplex) would not have given rise to active siRNAs.

For all the reasons previously presented and those presented here in, the applicants respectfully request reconsideration and withdrawal of this obviousness rejection.

If there are any questions or comments regarding this Response or application, the Examiner is encouraged to contact the undersigned attorney as indicated below.

Respectfully submitted,

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